Systematic Review

The efficacy of manual therapy and exercise for different stages of non-specific low back pain: an update of systematic reviews

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Objective: to review and update the evidence for different forms of manual therapy (MT) for patients with different stages of non-specific low back pain (LBP).
Data sources: MEDLINE, Cochrane-Register-of-Controlled-Trials, PEDro, EMBASE.
Method: A systematic review of MT with a literature search covering the period of January 2000 to April 2013 was conducted by two independent reviewers according to Cochrane and PRISMA guidelines. A total of 360 studies were evaluated using qualitative criteria. Two stages of LBP were categorized; combined acute–subacute and chronic. Further sub-classification was made according to MT intervention: MT1 (manipulation); MT2 (mobilization and soft-tissue-techniques); and MT3 (MT1 combined with MT2). In each sub-category, MT could be combined or not with exercise or usual medical care (UMC). Consequently, quantitative evaluation criteria were applied to 56 eligible randomized controlled trials (RCTs), and hence 23 low-risk of bias RCTs were identified for review. Only studies providing new updated information (11/23 RCTs) are presented here.
Results: Acute–subacute LBP: STRONG-evidence in favour of MT1 when compared to sham for pain, function and health improvements in the short-term (1–3 months). MODERATE-evidence to support MT1 and MT3 combined with UMC in comparison to UMC alone for pain, function and health improvements in the short-term.
Chronic LBP: MODERATE to STRONG-evidence in favour of MT1 in comparison to sham for pain, function and overall-health in the short-term. MODERATE-evidence in favour of MT3 combined with exercise or UMC in comparison to exercise and back-school was established for pain, function and quality-of-life in the short and long-term. LIMITED-evidence in favour of MT2 combined with exercise and UMC in comparison to UMC alone for pain and function from short to long-term. LIMITED-evidence of no effect for MT1 with extension-exercise compared to extension-exercise alone for pain in the short to long-term.
Conclusion: This systematic review updates the evidence for MT with exercise or UMC for different stages of LBP and provides recommendations for future studies.

Keywords: Non-specific low back pain, Manual therapy, Spinal manipulation, Efficacy, Randomized controlled trials

Introduction

After headaches and chronic fatigue, low back pain (LBP) is the most reported complaint, with more than 80% of the population reporting LBP at some point in their life.[1,2] In developed countries, LBP has enormous and growing indirect and direct costs for society and public health organizations.[3,4]

The majority of LBP cases are described as non-specific as there is no identifiable pathology on radiological imaging.[2] Indeed there is a poor correlation between findings on radiological imaging and symptoms, with a radiological diagnosis identified in only 15% of cases.[5–9] Hence, LBP is often a symptom of unknown origin and etiology.[2,5,10,11]

Many factors have been identified as possible causes or contributing factors to LBP. For example nociceptive inputs, particularly in acute–subacute conditions from various spine structures can cause pain, including zygapophysial joints, intervertebral discs and sacroiliac joints.[5,12–14] In chronic LBP, psychosocial factors are of prime importance in explaining the prolongation of pain.[2,15,16] Additional factors linked to chronic

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LBP include obesity and physical deconditioning associated with sedentary lifestyles.[2,17] Moreover, genetic factors have been strongly linked to LBP through their influence on pain perception and psychosocial factors.[2,18]

In general terms, in the case of acute LBP, reports suggest that 75–90% of cases recover within 6 weeks irrespective of medical intervention, whereas up to 25% are at risk of developing chronic pain and disability.[1,2] Indeed, many individuals with LBP have a number of persisting or recurring symptoms.[1,5,8,19] Chronic LBP therefore represents a considerable challenge because recovery is unlikely to occur, despite considerable medical advances.[20]

In physical therapy practice, various forms of manual therapy (MT) are currently used to manage LBP.[7,21–23] Manual therapists use a range of treatment approaches including various passive techniques such as mobilization and manipulation as well as a variety of different forms of exercise. The use of these approaches, along with clinical reasoning based on the bio-psycho-social model, represents the essence of MT (www.ifompt.com).[24]

This systematic review (SR) focuses on the effects of commonly used MT approaches identified through a comprehensive evidence based search strategy of low-risk of bias clinical trials. Three categories of passive MT techniques are defined; MT1 (lumbopelvic manipulation: high-velocity-low-amplitude thrust) MT2 (non-thrust lumbo-pelvic mobilization and soft-tissue techniques),[25–27] and MT3 (combination of MT1 and MT2). We also considered passive MT techniques (MT1–3) combined or not with exercise (specific or general) or combined with usual medical care (UMC) (stay active, reassurance, education and medication).[11,27,28]

The popularity and use of MT for the management of LBP has grown, in part supported by the inclusion of MT in various clinical practice guidelines.[5,10,23,29] This is despite uncertainty regarding the levels of evidence for the effectiveness of different approaches in MT at different stages of LBP.[5,7,10,22,29–36]

Previous SRs have reported that in general terms, MT is considered better than a placebo treatment or no treatment at all for LBP.[7,30,35–40] These reviews failed to establish levels of evidence for other forms of treatment such as UMC or exercise in comparison to MT.[35,37,39,40] In addition, previous SRs have not investigated which MT approaches (MT1–3), when combined with UMC or exercise, are more effective for LBP. The present SR updates previous reviews, and is the first to focus specifically on different MT approaches for different stages of LBP. New findings, as well as new evidence to inform findings from previous systematic reviews,[41–45] are presented.

Methods

This SR was conducted in accordance with the PRISMA and Cochrane-Collaboration-Back-Review-Group (CCBRG) updated guidelines for SR.[46,47]

Search strategy

A literature search of randomized controlled trials (RCTs) published in English between 2000 and 2013, on the efficacy of MT in the treatment of LBP was conducted independently by two reviewers in four electronic databases: MEDLINE, Cochrane-Register-of-Controlled-Trials, PEDro, and EMBASE. The detailed search strategy in MEDLINE is presented in Appendix 1, and was adapted to search in the three other databases.

Based on information revealed in the titles and abstracts, a first selection of articles was performed using the inclusion criteria described below. A final selection was conducted after a blinded critical appraisal of the quality of the studies. A consensus was reached at each step (Fig. 1) on the studies to be included. In cases of disagreement, a third reviewer made the necessary decision.

Inclusion criteria

Study design

RCTs from the period of January 2000 to April 2013 were included only if (i) they presented a low-risk of bias, (ii) if LBP cases treated with MT were compared to a randomized control group receiving either no treatment, a placebo procedure, or another effective therapy for LBP and (iii) if the randomization methods were appropriate and clearly reported, with moreover (iv) a single (assessors blinded) or quasi-double-blind design (assessors and patients blinded).

Patients

LBP is distinguished on the basis of the duration of the pain episode: acute (<6 weeks), subacute (6–12 weeks) and chronic (>12 weeks).[2,29] However, this distinction may not be satisfactory and it has been argued that categorization should be on the basis of other factors including location, symptoms, duration, frequency, and severity.[48] In this SR, we used a combination of duration, location and symptoms to specify the study population:

- Studies were included if subjects were males and females aged between 18 and 60 years suffering from acute–subacute (0–12 weeks) or chronic (>12 weeks) LBP. Acute and subacute categories were combined because of their similarities in contrast to chronic LBP category, where psycho-social factors appear more important.[16,49,50]
- LBP is defined as pain in the lower back between the lowest ribs and inferior gluteal folds.[46,51] Given that people with LBP may present with radicular pain, LBP is defined according to the following Quebec-Task-Force (QTF) classification: (1) LBP alone (QTF 1), (2) LBP with radiating pain into the thigh but not below the knee (QTF 2), (3) LBP with nerve root pain

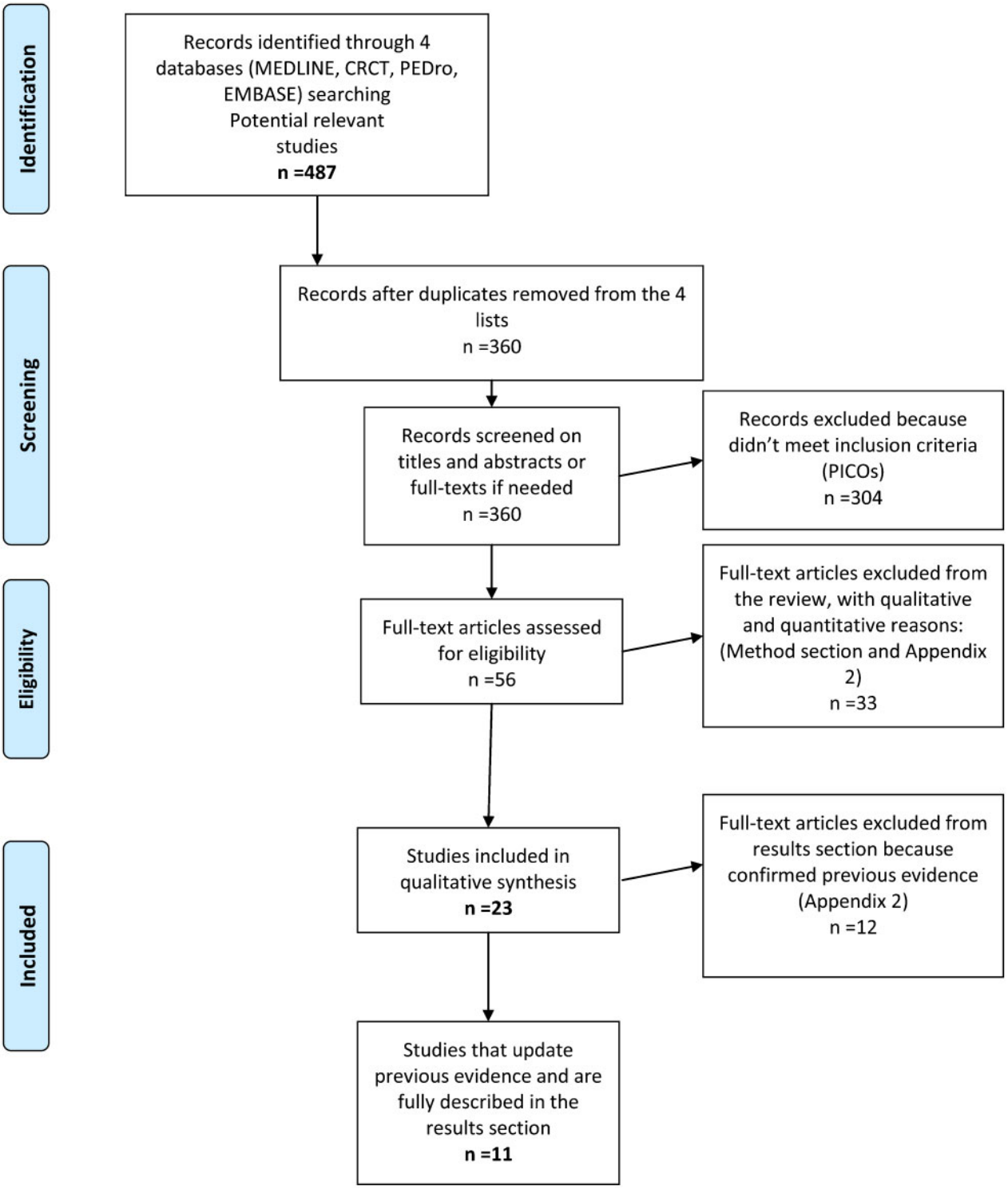

Figure 1 PRISMA flowchart of inclusion.

without neurologic deficit (QTF 3), or (4) LBP with nerve root pain with neurologic deficit (QTF 4).[52] In the present SR, only trials that contained patients in classes QTF 1–3 were included.

Interventions

Among the included trials, we considered three categories of the most common MT techniques represented in the intervention groups. MT1 comprised high-velocity-low-amplitude thrust of the lumbo-pelvic region with 'cavitation'.[7,21,22,27,37,53] MT2 comprised mobilization and soft-tissue-techniques including 'myofascial', 'myotensive' or 'harmonic' techniques on the lumbo-pelvic region.[22,27,37,54] MT3 comprised the combination of MT1 and MT2. Furthermore, sub-categorization of groups MT1–3 was based on the addition or not of exercises either specific (for example based on directional preference, stabilization, and motor control) or general (for example global strengthening, cardiovascular endurance, stretching and range-of-motion exercises) or UMC.[1,21,32,55]

Control groups

The control groups received no treatment, placebo, UMC, or exercise.

Outcome measures of effectiveness

The outcome measures were classified according to the CCBRG recommendations: pain, function, overall-health and quality of life (Table 1). Timing of the follow-up measurements was defined as very-short-term (end of treatment/discharge to 1 month), short-term (1–3 months), intermediate-term (3 months–1 year), or long-term (1 year or more).[46,47,51]

Quality assessment

Two independent reviewers assessed the risk of bias, methodological quality, data-extraction and clinical relevance of each trial.

Quantitative and qualitative criteria were assessed by applying the CCBRG criteria.[46,47] Quantitative risk of bias was assessed using an 11-point check-list (see Appendix 1).[47]

Qualitative criteria were: a clear distinction and separation between combined acute–subacute and chronic LBP categories at baseline; a detailed description of the MT intervention allowing the reviewers to classify the MT techniques according to MT1–MT3 classification system; and a single-blind (assessors blinded) or quasi-double-blind (assessors and patients blinded) design.

We considered as 'high-quality' those RCTs with quasi-double-blind designs that met at least 9/11 of the CCBRG criteria. 'Low-quality' RCTs status was assigned to studies of single-blind design with a minimum score of 7/11 (Tables 2 and 3). The dichotomy of classification into 'high' or 'low' qualities study is required when using the system of CCBRG to determine the strength of evidence (Table 1) and must be clearly described. To reduce the number of studies included in this SR, only studies that present new findings or update previous SR are described. Moreover similarly to another SR,[56] to facilitate clarity of presentation, RCTs were only included if they were of low-risk of bias, and either high quality (indicated by a 'A') or moderate quality (indicated by a 'B').

Strength of evidence and clinical relevance

Strength of evidence was determined by grouping similar 'Patients Interventions Comparisons Outcomes Study design' to provide an overall level of evidence (Table 1) on the efficacy of the MT techniques (Table 4). Based on CCBRG guidelines,[47,51] the effect sizes were independently collected or calculated by two authors, and used to assess the clinical relevance of MT interventions on outcome measures. We report the between groups means of difference (*MD=mean A–mean B*) or Cohen's standardized means of difference (*SMD=mean A–mean B/mean SD*). In this SR, the clinical relevance was determined by two conditions and scored by 'YES' in favour of the intervention group; if there were (i) significant difference between groups ($P<0.05$) associated (ii) with between groups effect sizes equal or superior to the minimal clinically important difference (MD) or moderate to large effect (SMD) on specific outcome measure (Tables 2 and 3).

Results

Two reviewers performed the initial selection of articles based on keywords. Upon discussion, the reviewers achieved consensus on inclusion of 56 trials that met the selection criteria based on their titles and abstracts. After critical appraisal of these 56 studies, 23 RCTs were retained (Fig. 1). Only 11/23 of these RCTs were found to have new evidence or updated previous SRs and are fully presented here. Appendix 2 and Table 4 present a summary of the remaining 12 RCTs that are not detailed in this results section.

The studies' characteristics and effect sizes on outcome measures are presented for acute–subacute (Table 2) and chronic LBP (Table 3). A qualitative SR was undertaken on the 11 low-risk of bias RCTs, five studies were classified as level A quality, and six as level B quality.

Table 1 Classification of outcome measures and Cochrane Collaboration Back Review Group (CCBRG) levels of evidence for evaluating interventions[46,47]

Outcome measures	Validated assessment tools
Pain	Visual Analogue Scale or Numerical Pain Rating Scale
Functional disabilities	Oswestry Disability Index, Roland Morris Disability Questionnaire, Fear Avoidance Belief Questionnaire, Disability Rating Index, or Patient Specific Function Scale
Overall-health improvement	Short form health survey
Quality of life	Patient Satisfaction with Care, Modified Zung Self-Rated Depression Score and State Trait Anxiety Inventory, return to work, sick leave, and medication use, adverse effects
Strength of evidence	Conditions description
Strong	Consistent findings from multiple 'high quality trials'=level A
Moderate	Consistent findings among multiple 'low quality trials' corresponding to moderate quality in this systematic review=Level B, and/or one level A
Limited	One level B
Conflicting	Inconsistent findings among multiple trials
No evidence	No trials

Table 2 Summary of articles for patients with acute–subacute LBP

AUTHORS sample size LBP status	Methodological quality of studies	Intervention + co-intervention	Comparison group + co-intervention	Outcomes measures of interest	Clinical relevance status on timing outcomes: between groups *P* value and effect sizes
Santilli *et al.*[57] (2006) *N*=102	Level A 10/11	MT1	Sham MT1	Local and radiating pain (VAS)	YES: at 45 days, $P<0.0001$ and MD=1.8; at 90 days, $P<0.0001$ and MD=1.8
ALBP 1–3	Care provider not blinded	5 times per week for maximum 4 weeks	5 times per week for maximum 4 weeks	Time to pain free status	YES: At 180 days, for local pain: $P<0.005$ and MD=22% and for radiating pain: $P<0.0001$ and MD 35%
				Overall-Health (SF-36)	NO: non-significant differences between groups
Hoiriis *et al.*[58] (2004) *N*=192	Level A 9/11	MT1+drug placebo	Sham MT1+ myorelaxant drug	Pain (VAS)	YES: 4 weeks, $P<0.05$ and SMD = 0.70
ALBP 1	Care provider not blinded? no intention-to-treat-analysis	7 sessions over 2 weeks for all groups	Sham MT1+ placebo drug	Functional disabilities (ODI)	NO: at 4 weeks, NS and SMD=0.35 (MT1 vs myorelaxant), 0.29 (MT1 vs placebo)
Von Heymann *et al.*[59] (2013) *N*=101	Level A 10/11	MT1+drug placebo	Sham MT1+ placebo drug	Pain (VAS)	YES: at 9 days between groups $P=0.013$ and MD=2.0
ALBP 1-2	Care provider not blinded	2–3 sessions over 1 week for all groups	Sham MT1+ diclofenac	Functional disabilities (RMDQ)	YES: at 9 days between groups $P=0.013$ and SMD=0.60
				Quality of life (SF-12, medication consumption, work-off)	NO: non-significant differences between groups
Bishop *et al.*[60] (2010) *N*=88	Level B 8/11	MT1 + UMC	UMC alone	Functional disabilities (RMDQ)	YES: at 16–24 weeks, $P=0.002$ and MD = 2.6
ALBP 1–2	Care provider and patients not blinded, no intention -to-treat-analysis	2–3 sessions over 4 weeks			
Cruser *et al.*[61] (2012) *N*=63	Level B 9/11	MT3+UMC	UMC alone	Pain (VAS)	YES: at 4 weeks: for pain now, $P=0.025$ and SMD=1.04; for pain typical, $P=0.020$ and SMD=0.88
ALBP 1–3	Care provider and patients not blinded	4 sessions over 4 weeks		Functional disabilities (RMDQ)	YES: at 4 weeks: $P=0.026$ and SMD=0.56

Note: ALBP=acute LBP; ASLBP=acute and subacute LBP: 1=LBP alone, 2=LBP radiating not below knee, 3= LBP radiating below knee without neurologic deficit. MT=manual therapy; MT1=spinal manipulation, MT2=spinal mobilization techniques; MT3=MT1+MT2. UMC=usual medical care. NS=non-statistically significant difference. SMD=between groups standardized mean of difference; MD=between groups mean of difference. Yes=$P<0.05$+moderate-large effect size (SMD, MD) in favour of MT. VAS=Visual Analogical Scale; NPRS=Numerical Pain Rating Scale; ODI=Oswestry Disability Index; RMDQ=Roland-Morris Disability Questionnaire; SF-36=short-form-health-survey.

Table 3 Summary of articles for patients with chronic LBP

AUTHORS Sample size LBP status	Methodological quality of studies	Intervention group + co-intervention	Comparison group + co-intervention	Outcomes measures of interest	Clinical relevance status on timing outcomes: between groups p-value and effect sizes
Ghroubi *et al.*[62] (2007) *N*=64 CLBP1	Level A 9/11 Care provider not blinded? for ITT	**MT1** 4 sessions per week over 1 month	**Sham MT1** 1 session over 1 month	Pain (VAS) Functional disabilities (ODI)	**YES:** at 4 weeks, $P<0.001$ and SMD=0.86; 8 weeks, $P<0.001$ and SMD=0.54 **YES:** at 8 weeks, $P<0.001$ and SMD=0.40
Senna *et al.*[63] (2011) *N*=93 CLBP1–2	Level A 10/11 Care provider not blinded	**MT1** non-maintained	**Sham MT1**	Pain (VAS)	**YES:** at 10 months, $P<0.005$ and MD=1.9
		MT1 maintained 3 sessions per week over 1 month for all groups, with 1 session/2 weeks during 9 months for **MT1** maintained		Functional disabilities (ODI) Overall-Health (SF36)	**YES:** at 10 months, $P<0.001$ and MD=18.9 **YES:** at 10 months, $P<0.001$ and MD=7.8
Niemistö *et al.*[32] (2003) *N*=204 CLBP1–3	Level B 8/11 Care provider and patients not blinded? for ITT	**MT2+exercise and UMC** 4 sessions of 60 minutes over 1 month	**UMC** 1 session of 60 minutes over 1 month	Pain (VAS) Functional disabilities (ODI)	**YES:** at 1 year, $P<0.001$ and SMD=0.60 **YES:** at 1 year, $P=0.002$ and SMD=0.45
Aure *et al.*[49] (2003) *N*=49 CLBP1–3	Level B 9/11 Care provider and patients not blinded	**MT3+exercise** 2 sessions of 45 minutes per week over 8 weeks for each group	**Exercise**	Pain (VAS) Functional disabilities (ODI) Quality of life: Return to work	**YES:** at 1 year: $P<0.05$ and MD=1.5 **YES:** at 1 year: $P<0.05$ and MD=9 **YES:** at 1 month, $P<0.01$ and MD=40%
Cecchi *et al.*[34] (2010) *N*=210 CLBP1–2	Level B 9/11 Care provider not blinded	**MT3+UMC** 4–6 sessions of 20 minutes/ week over 4–6 weeks	**Back school+UMC** **Physiotherapy+UMC** 15 sessions of 60' over 3 weeks	Pain (NPRS) Functional disabilities (RMDQ)	**YES:** at 1 year, $P<0.001$ and SMD=0.7 (MT3+UMC vs Back school+UMC), and SMD=1.1 (MT3+UMC vs physiotherapy +UMC) **YES:** at 1 year: $P<0.001$ and SMD =0.7 (MT3+UMC vs Back school+ UMC) and SMD=0.73 (MT3+UMC vs physiotherapy+UMC)
Rasmussen *et al.*[64] (2008) *N*=72 CLBP1–3	Level B 8/11 No for patient and care provider blinded and? for ITT	**MT1+extension exercises** 3 sessions over 1 month+ everyday exercise over 1 month.	**Extension exercises alone** Everyday exercise over 1 month	Back and leg pain (VAS)	NO: at 1 month and 1 year, NS differences for all outcomes measures

Note: CLBP=chronic LBP: 1=LBP alone, 2=LBP radiating not below knee, 3=LBP radiating below knee without neurologic deficit. MT=manual therapy, MT1=spinal manipulation, MT2=spinal mobilization techniques, MT3=MT1+MT2, MT3+specific and general exercises. UMC=usual medical care. NS=non-statistically significant difference. SMD=between groups standardized mean of difference, MD=between groups mean of difference. Yes=$P<0.05$+moderate-large effect size (SMD, MD) in favour of MT. VAS=Visual Analogical Scale, NPRS=Numerical Pain Rating Scale, ODI=Oswestry Disability Index, RMDQ=Roland-Morris Disability Questionnaire, SF-36=short-form-health-survey.

Table 4 Summary findings from systematic review for MT combined or not with exercise or usual medical care for LBP. Strength of new and updated evidence is shown in underlined and in bold text. Confirmation of previous evidence shown in bold text

Categories of MT interventions vs comparison group	Quality of evidence (A=high; B=moderate)	Strength of evidence for interventions
ACUTE (<6 weeks) and SUBACUTE (6–12 weeks) LBP		
MT1 vs Sham MT1	3 RCTs, Level A[57–59] *n*=395	STRONG evidence in favour of MT1 in comparison to sham MT1 for acute LBP, for PAIN, function, overall-health and quality of life improvements in the short-term (<3 months).
MT1 and MT3 combined with UMC vs UMC alone	2 RCTs Level B[60,61] *n*=151	MODERATE evidence in favour of MT1 and MT3 combined with UMC in comparison to UMC alone for PAIN, functional improvement and quality of life from very-short to short-term in patients with acute LBP.
MT1 with ROM exercise vs MT2 with exercise or exercise alone	2 RCTs Level B *n*=243 (Cleland *et al.*, 2009; Childs *et al.*, 2004)	MODERATE evidence in favour of MT1 with exercise as compared to MT2 with exercise or exercise alone for pain relief and function improvement at very-short-term and short-term. Functional improvement is also present at intermediate-term (6 months) in a specific subgroup of patients with acute–subacute LBP.
MT3 combined with exercise 'early' vs the same intervention 'delayed'	1 RCT Level B *n*=102 (Wand *et al.*, 2004)	LIMITED evidence in favour of an early intervention of MT3 combined with exercise in comparison to the same intervention delayed, on functional status and overall improvement at very-short-term and on overall improvement at intermediate-term in patients with acute LBP.
MT3 with UMC vs UMC alone	2 RCTs Level B *n*=339 (Curtis *et al.*, 2000; Juni *et al.*, 2009)	MODERATE evidence for no difference between MT3 combined with IMC in comparison to UMC alone, for pain reduction, functional recovery, and improvement in quality of life for very-short to intermediate-term in acute LBP.
MT3 combined with exercise vs UMC alone	1 RCT Level B *n*=402 (Hay *et al.*, 2005)	LIMITED evidence for no difference between MT3 combined with exercise vs UMC alone in terms of pain reduction and improvements of function from short to long-term in patients with acute–subacute LBP
MT2 vs Sham ultra sound	1 RCT Level A *n*=240 (Hancock *et al.*, 2007)	MODERATE evidence for no difference between MT2 and sham ultra sound in terms of pain reduction and functional improvements from very-short to short-term in acute LBP population.
MT3 combined with interferential therapy vs MT3 or interferential therapy alone	1 RCT Level B *n*=240 (Hurley *et al.*, 2004)	LIMITED evidence for no difference between MT3 associated with interferential therapy and MT3 alone or interferential therapy alone in terms of pain reduction, functional improvements, and quality of life improvement in patients with acute–subacute LBP.
CHRONIC LBP (>12 weeks)		
MT1 vs Sham MT1	2 RCTs Level A[62,63] *n*=157	MODERATE-STRONG evidence in favour of MT1 as compared to sham MT1, in terms of pain reduction, functional improvements and overall-health improvement at SHORT-term to INTERMEDIATE-term in patients with chronic LBP.
MT3 combined with exercise or with UMC vs exercise alone and back school	2 RCTs level B[34,49] *n*=259	MODERATE evidence in favour of MT3 combined with exercise or with UMC as compared to exercise alone and back school in terms of pain and function and quality of life improvement from short to long-term in patients with chronic LBP.

Table 4 Continued

Categories of MT interventions vs comparison group	Quality of evidence (A=high; B=moderate)	Strength of evidence for interventions
MT2 combined with exercise and UMC vs UMC alone	1 RCT Level B[32] *n*=204	LIMITED evidence in favour of MT2 combined with exercise and UMC in comparison to UMC alone in terms of pain reduction and function improvement from short to long-term in patients with chronic LBP.
MT1 with extension exercise vs extension exercise alone	1 RCT Level B[64] *n*=72	LIMITED evidence for no difference between MT1 combined with extension exercise in comparison to extension exercise alone in improving pain in the short-term and long-term in patients with chronic LBP.
MT2 vs UMC MT2 vs acupuncture	1 RCT Level B *n*=262 (Cherkin *et al.*, 2001)	LIMITED evidence in favour of MT2 as compared to UMC and acupuncture in terms of pain, function, and quality of life from short-term to long-term in patients with chronic LBP.
MT3 vs exercise	2 RCTs Level B *n*=452 (Ferreira *et al.*, 2007; Critchley *et al.*, 2007)	MODERATE evidence for no difference between interventions in terms of pain reduction, functional recovery and quality of life improvement in patients with chronic LBP.
MT3 vs Sham MT3	1 RCT Level A *n*=91 (Licciardone *et al.*, 2003)	MODERATE evidence for no difference between interventions in terms of pain reduction, functional improvement, and patient satisfaction with care in very short-term and intermediate-term for patients with chronic LBP.

Note: MT=manual therapy; MT1=manipulation; MT2=mobilization and soft-tissue-techniques; MT3=MT1+MT2. UMC=usual medical care; exercise=specific and/or general exercise.

Effects of interventions on acute and subacute LBP

MT versus sham-MT

Santilli *et al.*,[57] Hoiriis *et al.*,[58] and von Heymann *et al.*[59] (studies rated as level A quality) assessed the effects of MT1 in comparison to sham-MT1 in patients with acute LBP.

Santilli *et al.*[57] compared lumbo-pelvic rotational manipulation toward the pain-free direction to simulated manipulation not following any specific pattern and not involving rapid thrust. The frequency of treatment was 5 days per week until pain relief occurred or up to a maximum of 20 sessions of 5 minutes. For LBP up to 3 months, MT1 was more effective in decreasing local pain, radiating pain, and the duration of pain with clinical relevance ($P<0.0001$ and mean of difference of 1.8). No statistically significant differences were found for overall-health improvement and psychosocial outcomes. At 6 months, the percentage of pain-free patients was significantly higher in the MT1 group with mean difference of 22% for local pain ($P<0.005$) and of 35% for radiating pain ($P<0.001$). Two patients, one in MT1 and one in sham-MT1, were dissatisfied with treatment and stopped.

Hoiriis *et al.*[58] investigated the effects of lumbo-pelvic manipulation in prone or side-lying position combined with a drug placebo, in comparison to sham-MT1 combined with a muscle relaxant or with a drug placebo. Sham-MT1 consisted of manual light pressure on the lumbar spine in both positions (prone and side-lying). All groups received eight visits over 2 weeks and showed significant improvements in pain relief and disability ($P<0.0001$) and depression scores ($P<0.0001$). Clinically relevant differences between groups could only be identified in favour of the intervention group for pain relief in the very short term with $P<0.05$ and standardized mean difference of 0.70. However, further evaluation revealed that the perception of true MT was significantly higher ($P<0.05$) in the intervention group than in either of the two control groups. Indeed, the sham maneuver did not closely approximate the manipulation technique.

von Heymann *et al.*[59] explored the efficacy of lumbo-pelvic rotational manipulation in side-lying position and placebo-diclofenac in comparison to Sham-MT1 with diclofenac or placebo-diclofenac. Sham MT1 was performed using real manipulation in a prone position but at the incorrect location (i.e. on a non-dysfunctional sacro-iliac-joint) to mimic as closely as possible the intervention being tested. This sham procedure is not supposed to have any influence on the lumbar dysfunction and is not believed to harm the patient. All groups received 2–3 visits over a 1 week period. There was a clear and clinically relevant difference at very-short-term follow up (9 days) between the groups ($P=0.013$), the intervention

group showed a standardized mean difference of 0.60 on functional improvement with similar result for pain and quality of life. No adverse effects or harm were reported in this study. These results suggested that real MT1 had clinically superior effects than NSAID and placebo interventions.

MT with UMC versus UMC alone

Bishop *et al.*[60] and Cruser *et al.*[61] (studies rated as level B quality) compared respectively MT1 (2–3 sessions per week over four weeks) and MT3 (1 session per week over four weeks) combined with UMC, to UMC alone in patients with acute LBP from QTF 1–2.

Bishop *et al.*[60] reported clinically relevant differences in favour of the intervention group in terms of functional improvement ($P=0.002$ and mean difference of 2.6) at 16 and 24 weeks, but there were no significant differences for pain and physical functioning. In the short-term (4 weeks), Cruser *et al.*[61] determined clinically relevant differences in favour of MT3 compared to UMC alone for pain now ($P=0.025$ and SMD of 1.04) and pain typical ($P=0.020$ and SMD of 0.88) and a standardized mean difference of 0.56 for function associated with significantly greater satisfaction with treatment and overall-health improvement ($P<0.01$). The authors concluded that compared to UMC, MT1[60] and MT3[61] combined with UMC provides clinically greater improvement in function and pain relief.

Effects of interventions on chronic LBP

MT versus sham-MT

Ghroubi *et al.*[62] and Senna *et al.*[63] (studies rated as level A quality) investigated, respectively, the effectiveness of MT1 in a side-lying position (painful side-up) and MT1 in supine position (toward the painful side), as compared to sham-MT1 (mimic of lumbo-pelvic manipulation without final impulsion to provide minimal likelihood of therapeutic effect); on pain, function and overall health in patients with chronic LBP from QTF 1–2. True-MT1 of 4 sessions spread over one month for Ghroubi *et al.*,[62] or 16 sessions over 1 month for Senna *et al.*,[63] led to significant improvements for pain ([Ghroubi *et al.*[62] reported standardized mean difference of 0.86 at 4–8 weeks with $P<0.001$]; [Senna *et al.*[63] reported mean difference of 1.9 at 10 months with $P<0.005$]), for functional outcomes ([Ghroubi *et al.*[62] reported standardized mean difference of 0.40 at 4–8 weeks with $P<0.001$]; [Senna *et al.*[63] reported mean difference of 18.9 at 10 months with $P<0.001$]). Only Senna *et al.*[63] reported an overall-health improvement of mean difference of 7.8 at 10 months ($P<0.001$). The authors[62,63] concluded that MT1 is clinically effective in treating patients with chronic LBP in the short-term, but to obtain long-term benefit on all outcome measures requires maintenance of MT1 every 2 weeks.[63]

MT combined with other interventions

Niemistö *et al.*[32] (rated as level B quality) investigated the effects of combined MT2 (myotensive lumbo-pelvic mobilization techniques) with exercises (stabilizing exercise to correct lumbo-pelvic rhythm) and UMC in comparison to UMC alone (patient education, stay active approach, ergonomic instruction, home general exercises, and educational-booklet) in patients with chronic LBP from QTF 1–3. They found that the intervention group provided clinically relevant improvements in pain relief ($P<0.001$ and standardized mean difference of 0.60) and function ($P=0.002$ and standardized mean difference of 0.45) from the short to long-term (up to one year). However, there were no significant differences between the groups in terms of the quality-of-life and medical costs.

Aure *et al.*[49] (rated as level B quality) evaluated the effectiveness of MT3 (consisting of mobilization and rotational manipulation in side-lying position from T10 to the pelvis) combined with specific and general exercise in comparison to exercises only in patients with chronic LBP from QTF 1–3. Both groups received 16 sessions of 45 minutes over 8 weeks. The results showed statistically significant improvements in terms of pain reduction and function in both groups. However, there was a greater improvement in all outcome measures for the intervention group leading to clinically relevant differences in the very-short to long-term on pain (at one year: $P<0.05$ and mean difference of 1.5) and functional improvement (at one year: $P<0.05$ and mean difference of 9), as well as for return to work rate (at 2 months; $P<0.01$ mean difference of 40%).

Cecchi *et al.*[34] (rated as level B quality) compared one group receiving MT3 combined with UMC, to another group receiving back-school with UMC to another group receiving individual physiotherapy (passive and assisted mobilization, active exercises, massage, and proprioceptive-neuromuscular-facilitation) with UMC in patients with chronic LBP of type QTF 1–2. The results showed that MT3 led to clinically relevant decrease in pain (at 12 months: $P<0.001$, standardized mean of difference of 0.7 and 1.1) and a greater functional recovery (at 12 months: $P<0.001$, standardized mean of difference of 0.70 and 0.73) than the two control groups at long term. However, the intervention group (MT3) received significantly more treatment than the two control groups at follow-up. Pain recurrence and drug intake were also significantly reduced in the MT3 group ($P<0.001$).

Rasmussen *et al.*[64] (rated as a level B quality) compared the effects of combined MT1 (in a side-lying

position at the lumbar level of reduced movement) with exercises (two different extension exercises performed as often as possible during the day and at least once per hour), to the extension exercises alone in patients with chronic LBP classified as QTF 1–3. Both groups showed clinically relevant back and leg pain reduction, and no difference between the groups could be observed at the one month and one year follow-ups. Importantly, four patients in the intervention group and three in the control group reported worsening of back pain after 4 weeks, 3 months and one year.

Discussion

The purpose of this SR was to assess and update the evidence pertaining to the effectiveness of different MT approaches in isolation or when combined with exercise or UMC in the management of LBP. Thus, this SR deviates and provides clinicians and researchers with new information compared with other recent high quality SRs[41,43,45] which are focused more on manipulation. A detailed summary of these updated findings, as well as the strength of their evidence and level of agreement with existing studies, are presented in Table 4.[7,30,35–38,41,43,45]

In comparison to recent SRs,[36,41,43,45] the present results highlight a number of new issues in the management of LBP with MT:

Firstly, in comparison to previous reports of limited-evidence[41,43] showing no-difference between true and sham manipulation, the results of this SR show moderate to strong evidence[57–59,62,63] for the beneficial effects of MT1 in comparison to sham-MT1. These differences are demonstrated in terms of pain relief, functional improvement, and overall-health and quality of life improvements in the short-term for all stages of LBP.

Secondly, in patients with acute–subacute LBP, in contrast to the previous reports of limited evidence of no-difference for manipulation combined with other interventions,[41] we determined moderate-evidence[60,61] to support MT1 and MT3 combined with UMC, in comparison to UMC alone, for pain, function, overall-health and quality of life.[60,61]

Thirdly in patients with chronic LBP, in contrast to the previous reports of varying quality evidence (ranging from limited to strong) that manipulation has short term efficacy when combined with other interventions,[43] we found moderate evidence[34,49] in support of the use of MT3 combined with exercises or UMC, in comparison to exercise alone or back-school, for pain, function and return to work from short to long-term. In addition limited evidence[32] supports the use of MT2 combined with exercises and UMC, in comparison to UMC alone, for pain and function from short to long-term. Finally, there is limited evidence of no-difference in efficacy for MT1 combined with extension-exercises, in comparison to extension-exercises alone for pain.[64]

The highest quality clinical research study is the conventional RCT. These studies have good internal validity but at the expense of external validity. An alternative for 'real world' application is a pragmatic RCT which has good external validity but poor internal validity.[65] Pragmatic clinical trials are becoming a frequently used tool to evaluate complex interventions.[66] Another possibility is to extend the conventional RCT to retain some of its key advantages (e.g. Cochrane criteria shown in Appendix 1), and use a 'quasi-double-blind' design to make a realistic compromise between internal and external validity. The CONSORT guidelines should also be considered to develop high quality study designs.[67]

One of the key issues in MT research is developing a plausible placebo or sham technique. A sham manipulation should be an appropriate placebo procedure because it mimics interaction between the intervention, the patient, the practitioner and the environment. Moreover, researchers need to conceptualize placebo not only as a comparative inert intervention, but also as a potential mechanism to partially account for treatment effects associated with MT.[68]

In the present SR, only five studies were placebo-controlled, four of them using sham adjustment,[31,57,58,62,63] while one used a real manipulation at the incorrect spinal level to achieve an authentic placebo response.[59] Further research is required to identify a plausible placebo response.

In the majority of RCTs addressing the effectiveness of MT, LBP patients are treated as a homogeneous group while recent research suggests that people with LBP in fact comprise a heterogeneous group.[40,65,69] Consequently, the concept of subgrouping among people with LBP is growing in the MT literature.[65] Classification of patient into sub-groups and the application of specific MT interventions for each sub-group have been shown to be more efficient.[28,69–74] For example, a treatment based classification system to identify MT for people with LBP is one form of subgrouping.[28] The Start-Back-Tool is another approach that aims to sub-classify according to psychosocial issues, and has been found to be more effective than a non-subgrouping approach.[75,76] Moreover, the patients' beliefs and expectations regarding treatment effects of MT interventions has also shown to be an important predictor of treatment outcome.[77] Targeted MT for specific subgroups is important because of the heterogeneity of people with LBP, future clinical trials should address the 'wash-out' effect of applying treatments for unclassified LBP.[78]

In terms of quality of the MT management, MT should always be based on evidence-based-practice, which incorporates patient values (bio-psycho-social influences), clinical expertise and reasoning on part of the clinician, as well as the best available clinical research evidence.[5,79–81] It could also be useful to establish a minimum level of practical skills across the range of commonly used MT techniques to manage people with LBP, and to improve clinical reasoning skills dealing with the complexity of LBP.[65] Future studies should incorporate clinical expertise as a factor in treatment trials for LBP.

Limitations

The results of our SR should be interpreted in the light of some limitations. Firstly, there was heterogeneity in the RCTs evaluated in this study including the data presentation and outcome measures. Consequently, a meta-analysis enabling pooled statistics of effect was not possible. Furthermore, the strength of evidence comprising this SR is limited (particularly for the stronger level of evidence) due to the difficulty of a true double-blind study design and because of the limited number of high quality studies. Finally, only studies published in English from 2000 to 2013 were reviewed, leading to the possibility of relevant articles existing in other languages or before 2000.

Conclusions

This SR, based on low-risk of bias studies, has provided a comprehensive review of different MT approaches in patients with different stages of LBP, informing evidence-based-practice. Based on the results of this SR, a variety of manual procedures combined or not with other interventions, including exercise, may improve patient management. The summary findings of this review are both comprehensive and novel and may be used to guide clinical practice and future studies of this topic.

Recommendations for future research to investigate MT include pragmatic high quality RCTs to maximize the application of results to clinical practice and to reflect the complexity of clinical reasoning and multimodal management of MT. Future studies should also investigate targeted MT for specific subgroups of people with LBP, and continue to address the complex issue of the best placebo procedure in MT trials.

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Appendix 1

Search strategy in MEDLINE

In MeSH (MEDLINE), 'Manual Therapy' was used as a free-term. The result of the MeSH Heading was 'Musculoskeletal-Manipulations' and we added 'Low-Back-Pain' to the MEDLINE search box as follows: 'Musculoskeletal-Manipulations'[Mesh] AND 'Low-Back-Pain'[Mesh] AND ('humans'[MeSH-Terms] AND ('male'[MeSH-Terms] OR 'female'[MeSH-Terms]) AND Randomized-Controlled-Trial[ptyp] AND English[lang] AND 'adult'[MeSH-Terms] AND '2000/01/01'[PDat]: '2013/04/01'[PDat]).

Risk of bias assessment

Criteria list for methodological quality assessment from Cochrane Collaboration Back Review Group

A Was the method of randomization adequate? Yes/No/Don't know

B Was the treatment allocation concealed? Yes/No/Don't know

C Were the groups similar at baseline regarding the most important prognostic indicators? Yes/No/Don't know

D Was the patient blinded to the intervention? Yes/No/Don't know

E Was the care provider blinded to the intervention? Yes/No/Don't know

F Was the outcome assessor blinded to the intervention? Yes/No/Don't know

G Were cointerventions avoided or similar? Yes/No/Don't know

H Was the compliance acceptable in all groups? Yes/No/Don't know

I Was the drop-out rate described and acceptable? Yes/No/Don't know

J Was the timing of the outcome assessment in all groups similar? Yes/No/Don't know

K Did the analysis include an intention-to-treat analysis? Yes/No/Don't know

Operationalization of the criteria list

A: A random (unpredictable) assignment sequence. Examples of adequate methods are computer generated random number table and use of sealed opaque envelopes. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

B: Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.

C: In order to receive a 'yes,' groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurologic symptoms, and value of main outcome measure(s).

D: The reviewer determines if enough information about the blinding is given in order to score a 'yes.'

E: The reviewer determines if enough information about the blinding is given in order to score a 'yes.'

F: The reviewer determines if enough information about the blinding is given in order to score a 'yes.'

G: Cointerventions should either be avoided in the trial design or similar between the index and control groups.

H: The reviewer determines if the compliance to the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s).

I: The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a 'yes' is scored. (NB these percentages are arbitrary, not supported by literature).

J: Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.

K: All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.

Appendix 2 Studies that confirmed previous evidence (1) and studies that have been excluded from the SR (2)

1. Authors, Journals and quality score of included studies that confirmed previous evidence (Table 4)

ACUTE–SUBACUTE LBP	CHRONIC LBP
Childs *et al.*[1] Ann Intern Med (2004) level B (9/11)	Licciardone *et al.*[9] Spine (2003) level A (9/11)
Cleland *et al.*[2] Spine (2009) level B (8/11)	Cherkin *et al.*[10] Arch Intern Med (2001) level B (9/11)
Wand *et al.*[3] Spine (2004) level B (9/11)	Ferreira *et al.*[11] Pain (2007) level B (8/11)
Curtis *et al.*[4] Spine (2000) level B (8/11)	Critchley *et al.*[12] Spine (2007) level B (9/11)
Jüni *et al.*[5] Ann Rheum Dis (2009) level B (9/11)	
Hay *et al.*[6] Lancet (2005) level B (9/11)	
Hancock *et al.*[7] Lancet (2007) level A (10/11)	
Hurley *et al.*[8] Spine (2004) level B (9/11)	

2. Authors, Journals and qualitative and/or quantitative criteria for reason of exclusion

Bogefeldt *et al.*[13] Clin Rehabil (2008)	Outcome: only sick leave	Hertzman-Miller *et al.*[14] Am J Public Health (2002)	Patients: Mixed LBP status. Intervention: No for categorization of MT
Cairns *et al.*[15] Spine (2006)	Intervention: no for categorization of MT (6/11 Cochrane-list)	Hondras *et al.*[16] JMPT (2009)	Patients: Mixed LBP status
Chiradejnant *et al.*[17] Aust J Physiother (2003)	Patients: mixed LBP status (6/11 Cochrane-list)	Hsieh *et al.*[18] Spine (2002)	Patients: Mixed LBP status
Chown *et al.*[19] Physiother (2008)	5/11 Cochrane-list	Hurwitz *et al.*[20] Spine (2002)	Patients: Mixed LBP status. Intervention: No for categorization of MT
Eisenberg *et al.*[21] Spine (2007)	Intervention: no for categorization of MT	Kilpikoski *et al.*[22] Adv Physiother (2009)	Patients: Mixed LBP status
Ferreira *et al.*[23] Man Ther (2009)	4/11 Cochrane-list	Konstantinou *et al.*[24] JMPT (2007)	Patients: Mixed LBP status (6/11 Cochrane-list)
Flynn *et al.*[25] Spine (2002)	5/11 Cochrane-list	Kool *et al.*[26] Arch Phys Med Rehabil (2007)	Intervention: No for categorization of MT. Outcomes: no adequate outcomes
Geisser *et al.*[27] Clin J Pain (2005)	5/11 Cochrane-list	Miller *et al.*[28] JMMT (2005)	Intervention: No for categorization of MT
Giles and Muller[29] Spine (2003)	Patients: mixed neck and LBP	Mohseni-Bandpei *et al.*[30] Phys Ther (2006)	6/11 Cochrane-list
Goldby *et al.*[31] Spine (2006)	Intervention: no for categorization of MT (6/11 Cochrane-list)	Nagrale *et al.*[32] JMMT (2012)	Intervention: No for categorization of MT (neurodynamic)
Grunnesjo *et al.*[33] JMPT (2004)	'No' for co-intervention (steroid injections only in IG)	Niemisto *et al.*[34] Spine (2005)	Patients: Mixed LBP status. (6/11 Cochrane-list)
Haas *et al.*[35] Spine J (2004)	6/11 Cochrane-list	Paatelma *et al.*[36] J Rehabil Med (2008)	Patients: Mixed LBP status
Hagen *et al.*[37] Spine (2003)	Intervention: no for categorization of MT	Parkin-Smith *et al.*[38] Arch Phys Med Rehabil (2012)	'No' for assessor blinded (7/11 Cochrane-list)
Hallegraeff *et al.*[39] Percept Mot Skills (2009)	'No' for assessor blinded (7/11 Cochrane-list)	Rasmussen-Barr *et al.*[40] Man Ther (2003)	Patients : mixed LBP status (6/11 Cochrane-list)
Hancock *et al.*[41] Eur Spine J (2008)	'No' for assessor blinded (8/11 Cochrane-list)	Riipinen *et al.*[42] J Rehabil Med (2005)	Outcomes: no adequate outcomes
Hemmila *et al.*[43] JMPT (2002)	Intervention : no for categorization of MT (4/11 Cochrane-list)	Team UBT.[44] BMJ (2004)	Patients: Mixed LBP status

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